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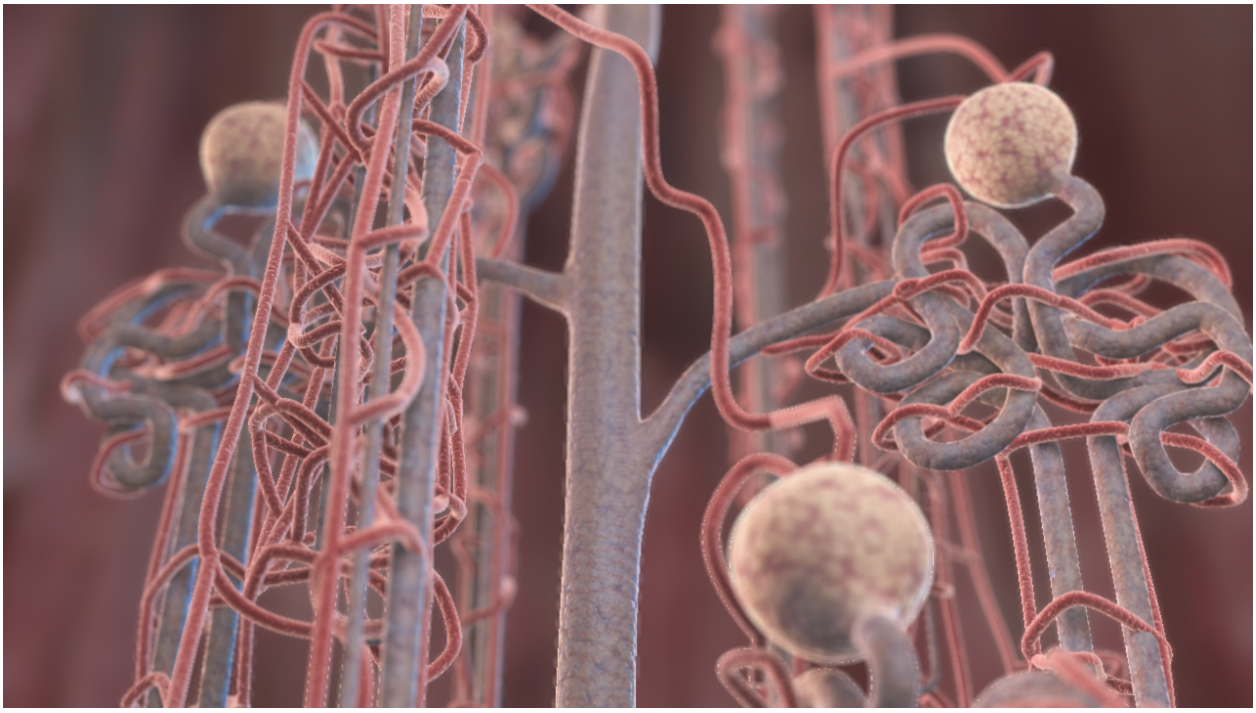

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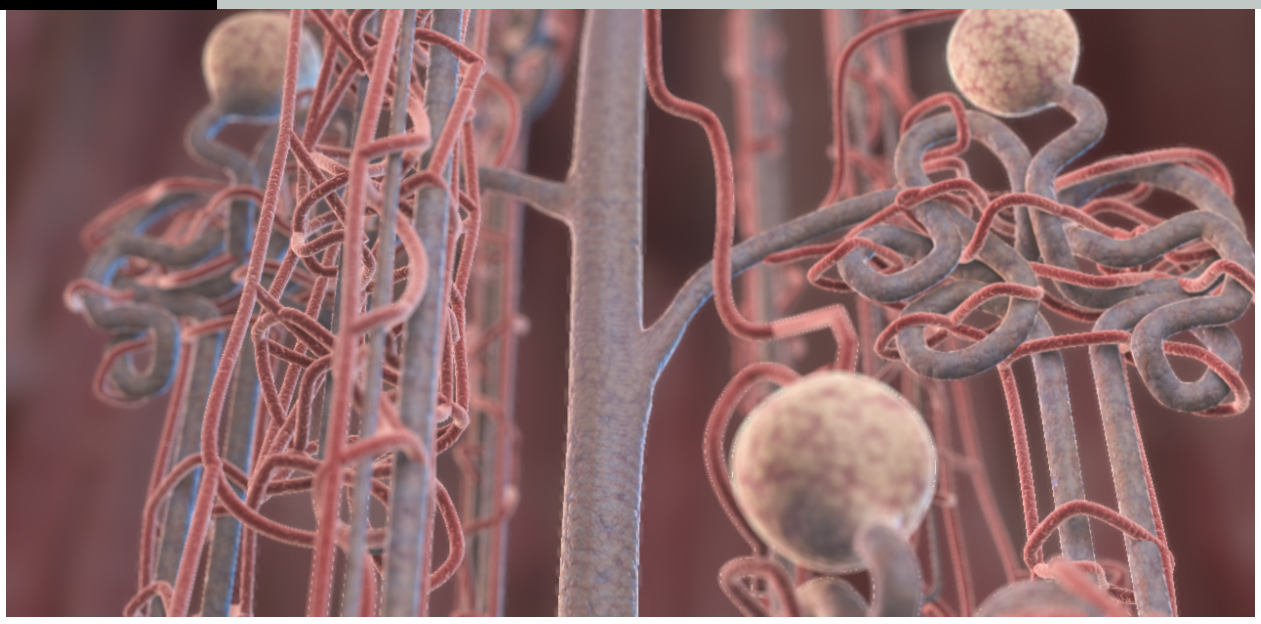

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Androgen and Androgen Receptor in Kidney Cancer

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Kidney cancer is one of the top ten most common cancers in men and women. There are four types of kidney cancer, including Renal Cell Carcinoma (RCC), Transitional cell carcinoma, renal sarcoma, and Wilm's tumor. The most common type of kidney cancers is renal cell carcinoma (RCC), with around nine out of ten kidney cancers being RCC (American Cancer Associate). Epidemiology studies have identified several risk factors associated with kidney cancer.[1] Among them, male gender is associated with twice incidence rate of RCC as female.[2] Androgen and Androgen Receptor (AR) are major factors contributing to male-gender-associated-diseases, such as prostate cancer,[3] suggesting that androgen and AR might be involved in RCC development and progression.

In contrast to the results of current epidemiological study, hormonal therapy had been evaluated in clinical trials for RCC patients in early decades.[4-8] Despite the discovery of the therapeutic effects of both progesterone and androgen in RCC patients, their therapeutic outcomes had not been appreciated.[9] Since androgen and AR are involved in male-gender-associated diseases, recent studies have switched the focus to target androgen and AR signaling in RCC. It was first disclosed that high AR expression is correlated with poor prognosis for RCC patients; signifying shorter overall survival, relapse-free survival, and cancer-specific survival.[10] However, another study suggests that AR is actually expressed in more than 90% of normal kidney human samples and that there are no differential AR expressions in normal male and female kidneys.[11] In addition, AR expression levels are inversely correlated with pT Stage and Fuhrman's Grade in RCC patients. This surprising result leads to further investigation of the transactivation activity of AR, as AR mainly exerts its function through transcriptional regulation of target genes.[12] Androgen treatment does not promote the transactivation activity of AR in commonly used RCC cell lines, such as CAKI-2 and OSRC-2, although AR expression could be detected in these cells. These interesting results bring up novel questions. How does male gender predispose RCC development if AR expression is reduced in RCC samples? Can AR be the therapeutic target even if RCC has AR expression without transactivation activity?

It has been demonstrated that targeting AR can be a potential therapy for RCC in pre-clinical model.[13] With *in vitro* malignant transformation assay, AR has been shown to promote normal human kidney epithelial cell transformation with more colony numbers and larger colony in the presence of carcinogen, ferric nitrilotriacetate. In addition, AR promotes cell growth of transformed kidney epithelial cells but not that of normal kidney epithelial cells. Furthermore, AR involves in cancer migration, invasion, and proliferation in RCC cell lines as determined by using overexpression and/or knockdown of AR in RCC cells with cancer progression assays. Using cancer-specific cDNA array, hypoxia-induced factor 2α (HIF2α) and Vascular Endothelial Growth Factor (VEGF) were identified to be the AR downstream targets responsible for AR-mediated RCC progression. By challenging RCC cells with HIF2α and VEGF inhibitors, AR-mediated RCC progressions could be abolished, suggesting that AR might modulate RCC

progression through HIF2α and VEGF signaling pathways.

To determine whether targeting AR can be a potential therapy for RCC, an AR degradation enhancer, ASC-J9®, was used to determine the effects of targeting AR on RCC progression in *in vitro* cell culture and in *in vivo* preclinical models, subcutaneous and orthotopic xenograft mouse tumor models. ASC-J9® treatment substantially reduces RCC proliferation, colony formation, migration, and invasion in *in vitro* cell assays. Targeting AR with ASC-J9® in RCC preclinical models also shows significant suppression of RCC tumor progression. In addition, ASC-J9 inhibits the expression of AR, HIF2α, and VEGF, suggesting that targeting AR may be a novel therapeutic approach for RCC patients.

Although androgen and AR signaling may be a potential therapy for RCC patients, it remains unclear as to why RCC have significantly less AR expression than normal kidney and why AR is negatively associated with RCC tumor stage. Future studies will be needed to explain these controversial observations.

DISCLOSURE

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Opinion

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Current Opinion in the Treatment of Diabetic Nephropathy

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KEYWORDS: Diabetic nephropathy; Autophagy; MicroRNA; Chronic inflammation; Nlrp3; mTOR; AMPK and Sirt1.

Diabetic nephropathy is a leading cause of end-stage renal failure. Approximately 20-40% patients with diabetes mellitus will develop nephropathy with a significant proportion requiring regular dialysis or kidney transplantation. The International Diabetes Federation estimates that 366 million people had diabetes worldwide in 2011 and 552 million people will have this disease by 2030.[1] The increasing incidence of diabetes elevates diabetic nephropathy to one of the most important current public health issues, representing a significant burden on the health system.[2] Despite current interventional strategies being intensively implemented, the number of patients with diabetes requiring renal replacement therapy for end-stage renal disease is growing.[3] Current treatments of diabetic nephropathy slow its progression,[3] so the optimal therapeutic strategy to arrest or reverse the nephropathy is needed urgently. As multiple risk factors and their interactions promote the development of diabetic nephropathy, targeting a single factor may be ineffective in the treatment of this disease; thus, optimal treatments by targeting multiple factors need to be developed to arrest or reverse the diabetic nephropathy.

The classical features of diabetic kidney include glomerular and tubular basement membrane thickening, and mesangial and interstitial expansion. There is deposition of extracellular matrix in both glomerular and interstitial compartments.[4] Due to increased matrix protein production and decreased protein degradation, over accumulation of collagen type I, III and IV, and fibronectin occurs in the mesangium and interstitium, which leads to decreased glomerular filtration, tubular injury and interstitial fibrosis. The mechanisms of the diabetic nephropathy have been largely investigated. It was well documented that chronic hyperglycaemia interferes with various intracellular processes including activation of protein kinase C, leads to generation of Advanced glycation end-products (AGEs) and reactive oxygen species, of inflammatory cytokines and chemokines and changes in cellular signaling pathways leading to dysregulation of transcription factors controlling the extracellular matrix homeostasis.[5-7] However, diabetic nephropathy is complex and multifactorial and the current therapies are largely ineffective, therefore there is increasing urgency to identify novel therapeutic targets that will allow more precise control over disease development and progression.

Current treatments of diabetic nephropathy involve the strict control of metabolic and hemodynamic abnormalities.[8,9] Glycaemic control, reducing albuminuria and management of hypertension are commonly used to limit the progress of diabetic nephropathy.[9] Despite of these strategies, the number of patients with diabetes that ultimately develop end-stage renal disease remains high. Novel agents to inhibit AGE-RAGE, PKC, TGFβ, oxidative stress, and fibrosis are under investigation.[8] In recent years, inflammatory pathways and inflammasome activation in renal disease has been recognised.[10,11] Micro-RNA based therapies have shown promise in ameliorating chronic renal disease;[12-16] and dysregulation of autophagy in the development of diabetic nephropathy has been reported.[17-21]

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CHRONIC INFLAMMATION IN DIABETIC NEPHROPATHY

Inflammation plays a central role in the progression of diabetic kidney disease.[11] Molecules integral to the inflammation pathways in diabetic kidney disease include transcription factors, pro-inflammatory cytokines, chemokines, adhesion molecules, Toll-like receptors, adipokines and nuclear receptors, which are all novel molecular targets for the treatment of diabetic kidney disease.[11] Comprehensive genomic profiling in diabetic kidneys identified the central role of proinflammatory pathways and the identified pathological gene assemblies resulting in renal inflammation, apoptosis and cell cycle arrest in progressive diabetic kidney disease.[22,23] Inflammasomes are key signaling platforms that detect pathogenic microorganisms and sterile stressors, and that activate the highly pro-inflammatory cytokines IL-1β and IL-18.[24] Nlrp3 is one such inflammasome that, once activated, Nlrp3 inflammasome activates caspase-1 and mediates the processing and release of cytokine IL-1β, amplifies the inflammatory response.[25] Once activated**,** Nlrp3 recruits the adapter ASC (apoptosis-related speck-like protein containing a caspase recruitment domain), which in turn recruits procaspase-1. Procaspase-1 auto catalyzes its cleavage and activation, resulting in maturation of the precursor forms of IL-1β and IL-18 into active proinflammatory cytokines and initiation of pyroptotic cell death.[26] The Nlrp3 inflammasome has been implicated in the pathogenesis of a wide variety of diseases including renal fibrosis. The Nlrp3 inflammasome has previously been reported to promote renal inflammation and contribute to chronic kidney disease.[27] Activation of the Nlrp3-inflammasome has been previously demonstrated in *in vitro* studies in endothelial cells and podocytes, in patients with diabetes, and in mouse models of diabetes.[28] It has been well summarized the recent findings: the Nlrp3 inflammasome is not limited by the traditional microbial stimuli of innate immunity and its connection with autophagy, apoptosis, fibrosis, and pro-inflammatory cytokines has broader implications for a variety of kidney diseases.[29] In a wide spectrum of glomerular and tubulointerstitial diseases, the Nlrp3 inflammasome is upregulated in both classical immune cells such as infiltrating macrophages and resident dendritic cells as well as in renal tubular epithelial cells, and even podocytes.[29] Inhibition of the Nlrp3 inflammasome ameliorates renal injury in a variety of animal models.[29] The deleterious effect of albuminuria on the proximal tubular epithelium and podocytes is, in part, mediated by inflammasome activation.[29] Therefore, developing strategies to target Nlrp3 inflammasome in diabetic nephropathy are warranted.

miRNAs IN DIABETIC NEPHROPATHY (DN)

Several miRNAs were reported to participate in the pathogenesis of DN, while others showed renal protective effects in diabetic nephropathy. To date, some miRNAs are displaying therapeutic potential with several in pre-clinical development. Thus, targeting miRNAs that are involved in diabetic nephropathy may have a good prospect in the treatment of the disease.[30,31] It was reported that the specific reduction of renal miR-192 decreases renal fibrosis and improves proteinuria, lending support for the possibility of an anti-miRNA-based translational approach to the treatment of diabetic nephropathy.[32] TGF-β1, a cytokine playing a central role in the development of diabetic nephropathy, reduced expression of the miR-29a/b/c/family, which targets collagen gene expression, and increased expression of ECM proteins.[33] miR-200a and miR-141 significantly impact on the development and progression of TGFβ-dependent EMT and fibrosis *in vitro* and *in vivo*.[34] It was also reported that overexpression of miR-21 in kidney cells enhanced, but knockdown of miR-21 suppressed, high-glucose-induced production of fibrotic and inflammatory markers. Thus inhibition of miR-21 might be an effective therapy for diabetic nephropathy.[35] One study has demonstrated that miR-21 overexpression can contribute to TGF-β1-induced EMT by inhibiting target smad7, and that targeting miR-21 may be a better alternative to directly suppress TGF-β1-mediated fibrosis in diabetic nephropathy.[36] Despite there are controversial reports about the role of miR-21 and miR-192 in the diabetic nephropathy,[37,38] miRNA-based therapies still hold great promise in ameliorating diabetic nephropathy. To date, the major obstacle to the therapeutic use of miRNAs is the delivery method. Systemic delivery of miRNAs or antagonistic miRs have been widely used, but lead to off-target effects, as this methodology may change the function of miRNAs in organs other than where pathology is targeted. To tackle this problem, kidney targeted delivery of exogenous miRNA is essential in the treatment of diabetic nephropathy.

AUTOPHAGY IN DIABETIC NEPHROPATHY

The development of metabolic diseases, such as type 2 diabetes and its complications are associated with alterations in several nutrient-sensing pathways.[17] One such nutrient-sensing pathway involves the mammalian Target of Rapamycin (mTOR), AMP-activated protein kinase (AMPK), and oxidized NAD- (NAD+-) dependent histone deacetylase (SIRT1), which are also recognized as important regulatory factors of autophagy under nutrient-depleted conditions.[17] Thus alteration of these pathways under diabetic conditions may impair the autophagic stress response, which may be involved in the development of diabetic nephropathy.[17] Indeed, treatment with rapamycin, an inhibitor of mTORC1, limits the development of diabetic nephropathy induced by Streptozotocin (STZ) in rats, which implicates a potential pathogenic role of the mTOR pathway in diabetic nephropathy.[39] One of the major upstream regulators of mTOR is AMP activated protein kinase (AMPK), a critical energy sensor. Many studies have shown that AMPK phosphorylation and activity are reduced in the renal cortex of kidneys from STZ-induced diabetic rats and db/db mice, while AMPK activators, resveratrol, metformin and AICAR attenuate renal hypertrophy, renal lipid accumulation and urinary albumin excretion.[20] SIRT1 has been shown to inhibit renal cell apoptosis, inflammation and fibrosis, and regulate lipid metabolism, autophagy, blood pressure and sodium balance.[40] As reviewed,[41] autophagy can be stimulated by multiple forms of cellular stress including growth factor deprivation, hypoxia and Reactive Oxygen

Species (ROS), which are common factors implicated in diabetic nephropathy. Hence targeting the autophagic pathway to activate and restore autophagy activity may be renoprotective. Fang, et al. reported high glucose/diabetes impaired autophagy in podocytes *in vitro* and in diabetic mice.[18] Tanaka, et al. present a compelling case for the need for studies addressing the roles of autophagy in diabetic nephropathy as these pathways are likely to be eminently suitable targets for novel therapeutic approaches.[17] Mitophagy dysfunction also contributes to the development of diabetic nephropathy. Mitochondria are the main energy-producing organelles in mammalian cells, but they also play a central role in cell injury and death signalling. Mitochondria are known to be a major intracellular source of ROS.[42] Under pathological conditions such as diabetes, uncoupling of oxidative phosphorylation and loss of mitochondrial membrane integrity induce excessive ROS production from the respiratory chain, while excessive ROS leads to further mitochondrial dysfunction and disruption.[43] Oxidative damage and the associated mitochondrial dysfunction may result in energy depletion, accumulation of cytotoxic mediators and cell death. Mitophagy, a biological process of autophagic removal of damaged mitochondria, is important as dysfunctional mitochondria may enhance cellular oxidative stress, generate apoptotic signals, and induce cell death. To date, autophagy is the sole known mechanism for mitochondrial turnover. Fragmented mitochondria are engulfed by autophogasomes *via* mitophagy and emerging evidence has suggested mitochondrial fragmentation is characteristic of renal diseases, including diabetic nephropathy.[42] In response to reduced cellular ATP, AMPK is activated, which phosphorylates ULK1 and ULK2 (two Atg1 homologues) to activate both general autophagy and mitophagy. In response to stress, induction of mitophagy results in selective clearance of damaged mitochondria in cells. Autophagic removal of damaged mitochondria requires two steps: induction of general autophagy and priming of damaged mitochondria for selective autophagic recognition, mediated either by the Pink1-Parkin signalling pathway or the mitophagic receptors Nix and Bnip3.[44] Dysfunction of mitochondria in diabetic kidneys has been well reviewed.[42,45] Studies from animal models indicate that disturbances in mitochondrial homeostasis are central to the pathogenesis of diabetic kidney disease.[46] Collectively, functionally restoring the autophagy and mitophagy in kidney may be an effective strategy to arrest the progression of diabetic nephropathy. However, to date there is not specific pharmacological activator or inducer of autophagy and mitophagy available.

In conclusion, the complications of diabetes mellitus, such as nephropathy, parallel its rapidly increasing incidence with resultant devastating personal and societal impacts. A successful continuum between innovative discovery science and rigorous translation of research findings is required to limit the development, and improve the outcomes of patients with existing diabetic nephropathy. However, diabetic kidney disease is complex and multifactorial and the current therapies are largely ineffective, therefore there is increasing urgency to identify novel therapeutic targets that will allow more precise control over disease development and progression. In addition to optimal control of hyperglycaemia, hypertension and albuminuria, novel strategies to target chronic inflammatory signalling pathways, restore function of autophagy and mitophagy, and kidney-specific deliver miRNA in kidney would be future directions for the treatment of diabetic nephropathy.

CONFLICTS OF INTEREST

We declare there are no conflicts of interest.

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Hypothesis

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A New Hypothesis: The Immunomodulatory Effects of Mesenchymal Stromal Cell Derived Extracellular Vesicles in Ischemic Kidney Injury Partly through Spleen

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ABSTRACT

Ischemic Reperfusion Injury (IRI) is a major reason for Acute Kidney Injury (AKI) in hospitalization patients and could continue to result in end-stage kidney fibrosis. Mesenchymal Stromal Cells (MSCs) are regarded as a promising therapeutic method for AKI, but the potential ethical and tumorigenesis problems of MSCs limit clinical use. Recently Extracellular Vesicles (EVs) that contained in the MSCs' condition medium were also found having a vital therapeutic effect in IRI induced AKI. As for the pluripotent prosperities of MSCs, MSC-EVs contain various bioactive substances that participate in the tissue repair and the immunomodulatory effect of MSC-EVs has been regarded as a crucial role in ischemic kidney injury and repair. However, the true mechanism still unknown. Based on existed facts, we hypothesized that the immunomodulatory effect of MSC-EVs in ischemic kidney injury partly through spleen.

KEYWORDS: Mesenchymal stromal cell; Extracellular vesicles; Ischemic kidney injury; Immunomodulatory.

ABBREVIATIONS: IRI: Ischemic Reperfusion Injury; AKI: Acute Kidney Injury; MSCs: Mesenchymal Stromal Cells; EVs: Extracellular Vesicles; I/R: Ischemia/Reperfusion; ICAM-1: Intercellular adhesion molecule-1.

INTRODUCTION

Ischemia/Reperfusion (I/R) injury could cause the intrinsic acute kidney injury (AKI) and lead to the kidney fibrosis in later stage.[1] Viable renal cells are unable to repair the necrotic tissues due to their limited capability of regeneration, which results in the damage of renal functions. Despite the renal replacement, there is no specific therapy to improve renal function has been found in decades. These facts reveal us to investigate new strategies to treat AKI.

In recent years, the MSCs-based therapy in AKI provides us a new way to protect the renal functions. MSCs from various sources (such as bone marrow, fetal membrane and adipose) in repairing kidney injury were reported,[2-4] however, the potential immune rejection, adipogenic differentiation and malignant transformation events of MSCs limit our clinical use. EVs contained in the MSC's condition medium could repair variety injured organs and also could alleviate I/R injury induced AKI.[5,6] EVs acquire the cell surface markers when they are released by different cells and could reach the target organs in body when they were injected intravenously. Our previous studies also found human umbilical cord mesenchymal cells derived EVs reached the spleen , lungs and injured kidney in a rat AKI model and it could attenuate the ischemic kidney injury,[7] which is consistent with the recent published results.[8] MSC-EVs could alleviate kidney injury and protect the renal functions in the different AKI animal models,

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and both the MSCs and MSC-EVs have the anti-inflammation characters *via* decreasing the pro-inflammation cells and factors in ischemic injured kidneys.[7,9-11] The inflammation level of ischemic kidney depends on the regulation of the whole body. As one of the most important immune organs in the body, spleen has the inflammatory cell regulation functions under different stresses and it could directly affect the circulating inflammatory mediators. The inflammatory cells in the spleen have an important role in the physiopathology of ischemic AKI, and it has been demonstrated that MSCs attenuate ischemic AKI trough immunomodulatory effects in a spleen depended manner, which means that MSCs would lose these effects without the spleen.[12] However, the possible mechanisms of MSC-EVs in IRI AKI remain unclear.

HYPOTHESIS

The effects of MSC-EVs in ischemic AKI are multiple and the immune systems have vital functions in kidney I/R injury. The immunomodulatory effects of MSC-EVs in ischemic kidney injury partly through spleen. (Figure 1).

Evaluation of the Hypothesis

The physiopathology of ischemic AKI is complex and the role of inflammation in AKI has been well known.[13,14] The alternation of inflammatory cells and factors in different milieus may exert different effects. In the initiation and extension of ischemic AKI, pro-inflammation cells are increased and activated in the injured kidney. Studies have shown that T cells are the key mediators in ischemic AKI and the regulation T cells (Tregs) have the reno-protective effects.[15,16] Pro-inflammation cells could directly kill the tubular epithelial cells or secrete pro-inflammatory factors to lead the kidney damages indirectly.[17-20] Then the inhibitions of some inflammatory pathways were used to attenuate organ I/R injury. Researchers have also found that it could significantly decrease the renal tubular apoptosis and protect the kidney functions in AKI animal models when depleting some inflammatory related cells and pro-inflammatory factors.[21,22]

Different tissue sources acquired MSCs and MSC-EVs are used to regulate inflammatory response in injured organs. MSCs could exhibit immunosuppressive or immunomodulatory properties by inhibiting T cells and NK cells.[23,24] The down-regulation of TNF-a, IL-6, macrophages and up-regulation of the IL-10, IL-4, Bfgf were also found after MSCs treatment in injured kidney.[25-28] What is more, in the acute lung injury mice model, MSCs derived EVs reduced the neutrophils and inflammation factors both in injured lungs and plasma, and the macrophage inflammation protein-2 in the injured lungs also changed.[29] The infiltration of different inflammatory cells in injured kidneys depends on the cells that transmigration across the vascular endothelium in serum. As one of the most important immune organ

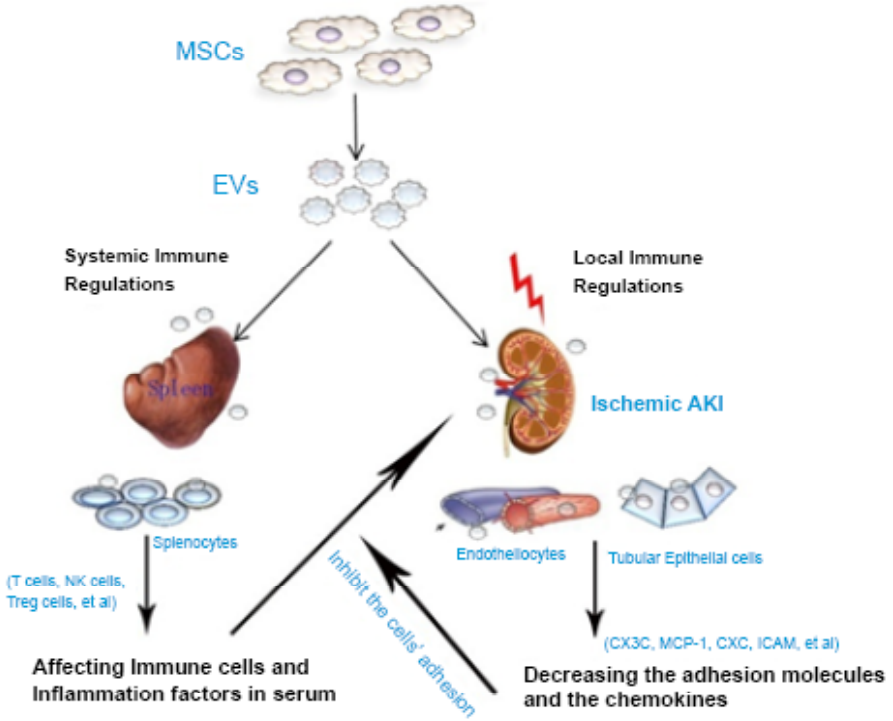

Figure 1: EVs derived from mesenchymal stromal cells have the therapy effects in AKI through accommodating both the systemic immune responses and chemokine in injured kidneys. After admination of MSC-EVs in ischemic kidney models, EVs could reach the targeted organs (spleen and injured kidneys) to change the systemic immune responses (such as change the phenotypes of T cells, NK cells, NKT cells or Tregs) and chemokine levels in injured kidneys (CX3C, ICAM-1, CXC, MCP-1, et al). Through the combined effects above, EVs ultimately lead to regulate inflammatory levels in the ischemic kidney and attenuate kidney injury.

in the body, spleen has the inflammatory cell regulation function under different stresses and it could directly affect the circulating mediators or signals. The immune cells in the spleen participate the physiopathology of AKI,[30,31] and Jie Hu, et al. also demonstrated that MSCs attenuate AKI by immunomodulatory effects in a spleen depended manner.[12] Meanwhile, the transmigration of inflammatory cells across the vascular endothelium into kidneys depends upon various adhesion molecules, chemokine and their receptors.[32] Studies have showed that a large number of chemokine like CCL2, CXCL8 are increased in kidney after ischemic AKI.[33] Moreover, activated tubular epithelial cells could express Intercellular adhesion molecule-1 (ICAM-1) and P-select in to interact with the neutrophils, monocytes and T cells.[34] These factors are generated by the tubular epithelium or vascular endothelial cells in injured kidney to attract inflammatory cells. So both the immune cells in circulation systems and chemokines in injured kidneys determine the ultimate inflammation levels in injured organs.

EVs are small vesicles in the condition medium with an average about 100 nm sizes. So compared to MSCs, EVs could not only recognize the target cells *via* specific surface receptors, but also could reach various organs in body *via* circulation systems. After recognition of the target cells, EVs could change target cell phenotypes by delivering bioactive substances, such as proteins, mRNAs and miRNAs.[35,36] Researchers have proved that endothelial cell derived EVs are able to reprogram vascular cells by transfer mRNAs and MSC-EVs protect the kidney tubular cells by transfer related miRNAs.[37-39] Until now, various mRNAs in the MSC-EVs have been found, such as cell cycle related SUMO1, transcription factors related Interferon regulatory factor 6 and it also has the immune regulation related Interleukin 1receptor antagonist and Cytokine receptor-like factor 1.[38] What is more, several recent reports have demonstrated that the effect of EVs is limited not only to local kidneys but to other organs,[8,40] which may suggest the presence of a systemic effect of EVs in ischemic AKI. Based on the above facts, we hypothesize that MSC-EVs exist immunomodulatory effects in ischemic kidney injury and these effects partly through spleen.

However, there were still some questions for further detail research. First, there are many inflammatory cells in the physiopathology of ischemic AKI, any of these might be involved in EVs' therapy effects. In the previous studies, macrophages and T cells were involves in the protective role of MSCs in renal IRI.[12,41] As for the EVs derived from MSCs, we may focus these cells for the further research. Second, the inflammation related chemokine in ischemic kidneys are multiple, such as CX3C, CXC, MCP-1, et al. To ensure the main cells and (or) factors in this process is the next works. Third, how MSC-EVs change these cell phenotypes or proteins remains controversy. Some studies showed that EVs derived from various sources could horizontal transfer nuclear acids, functional proteins, bioactive membrane and other materials to target cells.[42,43] In our opinion any way cannot be excluded. All of these should be explicated in future research.

Consequences of the Hypothesis

Ischemic AKI is a serious condition that occurs in clinical treatment, and MSC-MVs provide the same or better therapeutic effect when compared to MSCs. In the previous studies researchers found that MSCs have the immunomodulatory effects in ischemic kidney injury in a spleen depended manner. As for the immunomodulatory effects of MSC-EVs in organ injury repair still unknown, so we hypothesize here that both systemic inflammatory cells and local kidney chemokines are regulated by MSC-EVs and these effects partly through spleen, which propose a new sight in MSC-EVs' treatment and supply the theoretical basis for the direction of clinical use.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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Research

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Comparison of Hospital-Acquired and Community-Acquired Acute Kidney Injury in Hospitalized Patients

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ABSTRACT

Introduction: Little is known about patients sustaining Acute Kidney Injury (AKI) in the Community Acquired Acute Kidney Injury (CA-AKI) and how this differs from AKI in Hospital Acquired Acute Kidney Injury (HA-AKI). The objective of this study is to compare epidemiology, clinical characteristics, etiologies, severity and outcomes of patients of these two categories.
Methods: A prospective study was conducted during seven months from September 2012 to March 2013 in Hassan II University Hospital including all patients admitted to different departments of the hospital and having AKI. AKI was verified by applying the Acute Kidney Injury Network (AKIN) criteria, and patients were categorized as CA-AKI if AKIN criteria were met at admission. While HA-AKI was defined as if AKIN criteria were met twenty-four hours or longer after hospitalization.
Results: Among the 210 patients with AKI, 157 were classified as CA-AKI (74.8%). There was no significant difference in age average and comorbidities between CA-AKI and HA-AKI. Dehydration and volume depletion were significantly more prevalent in patients with CA-AKI (47.7% *vs.* 34% for HA-AKI $p<0.04$). While HA-AKI was associated with a significantly higher prevalence of acute tubular necrosis than CA-AKI (50% *vs.* 3,8% in CA-AKI $p<0.0001$). Having the same severity of AKI, the two groups had sustained a high rate of residual renal failure. Also there were no significant differences between the numbers of patients requiring renal replacement therapy, and the length of hospital stay in both groups. The mortality in hospital was significantly higher in the HA-AKI group compared to AC-AKI group (39.6% AH-AKI *versus* 25.4% AC-AKI $p<0.03$).
Conclusion: This study highlights that risk factors for CA-AKI and HA-AKI are similar, with CA-AKI also being similar in patients with preexisting CKD, diabetes, heart disease, hypertension, and cancer. This highlights the clinical characteristics of people in the community who may benefit from more frequent blood tests in the event of an acute illness or medication change.

KEYWORDS: Acute kidney injury; Community acquired; Hospital acquired; Outcomes.

ABBREVIATIONS: AKI: Acute Kidney Injury; AKIN: Acute Kidney Injury Network; CKD: Chronic Kidney Disease; CA-AKI: Community Acquired AKI; sCr: serum Creatinine; HA-AKI: Hospital-acquired acute kidney injury; MDRD: Modification of Diet in Renal Disease; CRF: Case Report Form; ICU: Intensive Care Unit; CI: Confident Interval; ATN: Acute Tubular Necrosis; KDIGO: Kidney Disease Improving Global Outcomes.

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INTRODUCTION

Acute kidney injury (AKI) is defined as a rapid loss of kidney function and oliguria, which is associated with adverse patient outcomes.[1,2] AKI is frequently associated to care; it is estimated to occur in up to 15% of hospitalized patients and up to 60% of critically ill patients.[3-5] Despite substantial advances in renal replacement therapy and health care delivery, morbidity and mortality rates associated with AKI have remained high. However, our current understanding of the epidemiology of AKI and its impact on morbidity, mortality, cost of medical care, and development of Chronic Kidney Disease (CKD) is based almost exclusively on studies of patients who developed AKI while hospitalized (HA-AKI). However, some patients develop AKI prior to hospitalization, termed community acquired AKI (CA-AKI); the incidence of CA-AKI, the validity of the AKIN classification, and the impact of CA-AKI on patient outcomes are all not well studied. In this observational study, we compare clinical characteristics, etiologies, and outcomes of patients admitted to the hospital with community-acquired AKI in contrast to those who acquired AKI during their inpatient stay.

MATERIALS AND METHODS

Study Design

This is a prospective study, conducted during seven months from September 2012 to March 2013 in Hassan II University Hospital, Fez, Morocco.

Patients

We included all patients admitted to different departments of the university hospital and having acute kidney injury during the study period. Patient's inclusion was done by nephrologist after his/her requestor an increased serum creatinine among those patients.

Comparing Groups Definitions

AKI was defined according to the acute kidney injury network (AKIN) classification[6] (Table 1). Community-acquired acute kidney injury (CA-AKI) was defined as patients with sufficiently changed serum creatinine and urine output in order to meet AKIN criteria at the admission period (Table 1). Baseline serum Creatinine (sCr) values for patients with CA-AKI were determined through review of all sCr values taken from the patient (from the hospital or the community) during the preceding 12 months. Hospital-acquired acute kidney injury (HA-AKI) was defined as an increase in serum creatinine and/or oliguria, according to AKIN criteria, that occurred twenty-four hours or longer after hospitalization. Patients were identified as having HA-AKI if no AKI was apparent on admission to hospital, but AKI developed during their hospital stay. Baseline sCr for patients with HA-AKI was taken as sCr on admission and was confirmed to be representative of true baseline by review of results from 12 months earlier. When no baseline sCr was available, the percentage increase that defines AKI was calculated using the upper limit of normal laboratory reference range for sCr in men and women, respectively. Moreover, patients with unknown baseline values had sCr values charted after AKI resolution, which further enabled approximation of baseline sCr and confirmation of true AKI. This method of baseline sCr identification is recommended in the recent Kidney Disease Improving Global Outcomes (KDIGO) AKI guidelines.[7]

Stage	Serum creatinine criteria	Urine output criteria
1	Serum creatinine increase ≥26.5 µmol/l (≥0.3 mg/dl) OR increase to 1.5-2.0-fold from baseline	<0.5 ml/kg/h for 6 h
2	Serum creatinine increase >2.0-3.0-fold from baseline	<0.5 ml/kg/h for 12 h
3	Serum creatinine increase >3.0-fold from baseline OR serum creatinine ≥354 µmol/l (≥4.0 mg/dl) with an acute increase of at least 44 µmol/l (0.5 mg/dl) OR need for RRT	<0.3 ml/kg/h for 24 h OR anuria for 12 h OR need for RRT

Table 1: Acute Kidney Injury Network criteria.

Patients with preexisting chronic kidney disease (CKD) that sustained acute-on-chronic kidney injury were included. CKD was identified from blood tests indicating baseline eGFR<60 ml/min per 1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) equation.[8] Recovery from AKI was defined as achievement of sCr no longer in keeping with the definition of AKI in comparison to baseline sCr values.

Data Collection

Data were collected by nephrologists practicing in the university hospital of Fez using a Case Report Form (CRF) that was designed earlier for the study. Clinical data collected included admitting specialty, demographics, medications, organ specific complications, and comorbid conditions. Creatinine values within 6 months prior to admission and at admission, at peak, at discharge were recorded. Admission to an Intensive Care Unit (ICU), requirement for dialysis, in-hospital mortality, length of stay, causes of death, in-hospital renal recovery and discharge disposition were recorded. A presumed cause of AKI was assigned based on clinical judgment after review of the medical record.

Statistical Analysis

Statistical analysis was carried out using SPSS software, version 20. A descriptive analysis was performed, Continuous data was presented as mean and Standard deviation (m±Sd) and categorical data as a percent and 95% Confident Interval (CI). At the univariate analysis, proportions were compared between groups using a Pearson chi-squared test. Continuous data were compared using t-test when comparisons were between

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two groups.

Ethical Considerations

An informed consent for participating in the study was obtained for all patients. No invasive investigation means was used. The authors declare no conflict of interest.

RESULTS

We included 210 patients having AKI, aged 57.2±19.2 years with a sex ratio (M/F) of 1.13.

The main reasons for hospitalization were infections, uro-nephrologic diseases and digestive symptoms in respectively 18%, 16.7%, and 14% of cases. Patients were admitted at emergency services in 66% of cases, at ICU in 15% of cases and at others medical departments in 16% of cases. Six percent of AKI episodes were mild (AKI stage 1); whereas most patients (70%) had sever renal insufficiency (AKI stage 3), and 24% stage 2. Length of hospital stay was a mean of 12.5±13.5 days. The global mortality rate among all patients study was 29%. Among the 210 patients with AKI, 157 were classified as CA-AKI (74.8%), while 53 cases were classified as HA-AKI (25.2%). There was no significant difference in age average between CA-AKI and HA-AKI. Preexisting CKD was observed in 15.7% of patients with AKI, with similar proportions across the CA-AKI and HA-AKI groups (16.5% *versus* 13.2%; p=NS). Comparison of prevalence of various comorbid conditions in patients with CA-AKI and HA-AKI revealed approximately equal proportions of such diagnoses as diabetes, hypertension, heart disease and cancer. Table 2 compares the patient characteristics of patients with CA-AKI and HA-AKI. The physiologic characteristics of AKI were divided into three categories; prerenal, intrarenal, and post renal. Intrarenal causes of AKI accounted for a greater proportion of HA-AKI (49% *vs.* 36%; p< 0.05), while prerenal causes were more common among patients with CA-AKI (48% *vs.* 43%; p=NS). Dehydration and volume depletion were significantly more prevalent in patients with CA-AKI (47.7% *vs.* 34%; p<0.04). Also the number of CA-AKI patients with glomerulonephritis as the cause of AKI was significantly higher compared with HA-AKI (10.1% *vs.* 1.8%; p<0.04). CA-AKI was associated with a significantly lower prevalence of Acute Tubular Necrosis (ATN) than HA-AKI (3,8% *vs.* 50%; p<0.0001). The frequency of symptomatic congestive heart failure and obstructive uropathy was not significantly different between the two groups (Figure 1, Figure 2 and Table 3).

We have also investigated the data for acute mortality and short-term outcomes. Table 4 showed that the serum creatinine level at the admission was significantly higher in patients with CA-AKI compared to AH-AKI (62.5 mg/l *vs.* 42.6 mg/l

	IRA-AH (n=53)	IRA-AC (n=157)	P
Mean age+/- SD (yr)	52.4+/-19	58.8+/-19	NS
Preexisting CKD	7(13.2%)	26(16.5%)	NS
Diabetes	10(18.8%)	30(19.1%)	NS
Hyertension	10(18.8%)	29(18.4%)	NS
Heart failure	6(11.3%)	19(12.1%)	NS
Cancer	10(18.8%)	24(15.2%)	NS

Table 2: Characteristics of patients with CA-AKI and HA-AKI.

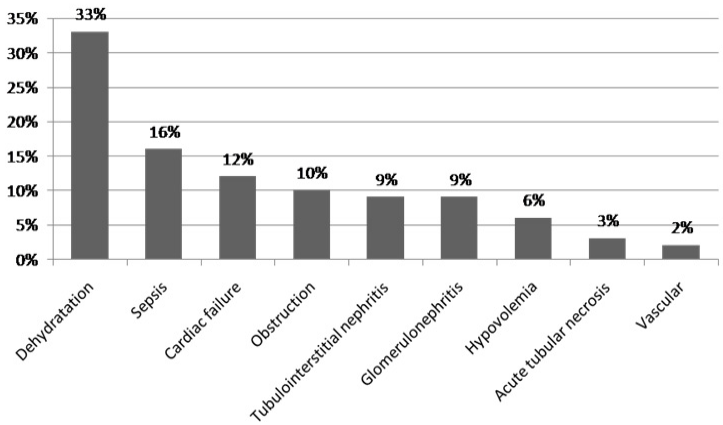

Figure 1: AC-AKI etiologies.

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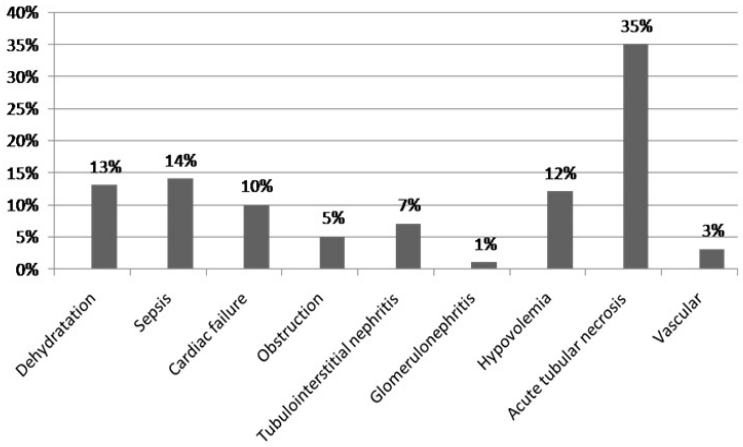

Figure 2: AH-AKI etiologies.

Etiology	AC-AKI (n:157)	AH-AKI (n:53)	P
ATN	4(3.8%)	27(50%)	<0.0001
Glomerulonephritis	16(10.1%)	1(1.8%)	0.042
Volume depletion	75(47.7%)	19(34%)	0.04

Table 3: Etiology of AC- AKI and AH-AKI.

p<0.01), Table 4 showed also no significantly differences between proportions of AKIN stages in the two groups compared. Short-term outcomes in patients with CA-AKI and HA-AKI are shown in Table 5. Having the same severity of AKI, the two groups had sustained a high rate of residual renal failure (77% AC-AKI *versus* 73% AH-AKI). Also there were no significant differences between the numbers of patients requiring renal replacement therapy in both groups (3.5% in the CA-AKI group and 1.8% in the HA-AKI group), and the length of hospital stay; the median stay in both patients with CA-AKI and HA-AKI was similar (12.5±14 days). However, mortality in hospital was significantly higher in the HA-AKI group compared to AC-AKI group (39.6% AH-AKI *versus* 25.4% AC-AKI; p<0.03).

DISCUSSION

Incidence and associated mortality risks of AKI in critically ill patients are well documented.[3,4,9,10] Increases in serum creatinine levels in non-critically ill hospitalized patients are also common and carry heightened mortality.[1,2,11,12] This has been attributed to the older age and increased number of comorbid conditions present in hospitalized patients with AKI. In contrast, studies describing incidence, risk factors, and outcomes of patients who sustain AKI in the community are limited. The current study found that CA-AKI was more common than HA-AKI, accounting for almost 80% of the patients with a diagnosis of AKI. That finding is consistent with two recent previous reports. Wonnacott, et al.[13] identified 686 patients who sustained AKI in the community. They compared this cohort with 334 patients who sustained AKI during a hospital stay. The incidence of CA-AKI was found at 86.2% in this study. Also Schissler, et al.[14] found higher incidence of CA-AKI at 80%. In two earlier studies, Obialo, et al.[15] performed a retrospective study of 100 African Americans with AKI in which 80% of patients had CA-AKI. Wang, et al.[16] reported that 60% of 211 Chinese patients with AKI had CA-AKI. The absence of a reliable baseline serum creatinine was a significant limitation in both those studies. The availability for a baseline creatinine in the current study allowed us to accurately identify patients with CA-AKI, to define the prevalence of CKD in our cohort, and to accurately classify the severity of AKI.

This study highlights that risk factors for CA-AKI and HA-AKI are similar, with CA-AKI also being similar in patients with preexisting CKD, diabetes, heart disease, hypertension, and cancer. This highlights the clinical characteristics of people in the community who may benefit from more frequent blood tests in the event of an acute illness or medication change.

CKD was previously defined as a risk factor for AKI, and a 15.6% prevalence of CKD in the current study supports those observations.[5,17] There was no difference in the prevalence

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	AC-AKI (n:157)		AH-AKI (n:53)		P
	n	%	N	%	
AKIN stage1	11	(7%)	2	(3.7%)	NS
AKIN stage2	38	(24%)	12	(22.6%)	
AKIN stage3	108	(68.7)	39	(73.5%)	
Admission sCr values (mean±SD) mg/l	62.5±57		42.6+/-33.8		<0.018

Table 4: Severity of CA-AKI and HA-AKI.

	AC-AKI (n:157)		AH-AKI (n:53)		p
	n	%	n	%	
Hemodialysis	35	(22.29%)	11	(20.7%)	NS
Residualrenalfailure	121	(77%)	39	(73%)	NS
Mortality	40	(25.4%)	21	(39.6%)	<0.03
Median length of hospital stay (days)	12.59+/-13.4(1-71)		12.4+/-14(1-81)		NS

Table 5: Outcomes of community- *versus* hospital-acquired AKI.

of patients with CKD between CA-AKI and HA-AKI patients in our study. We deduce that CKD is also an important risk factor for CA-AKI. In a previous study, patients with CKD were reported to experience more severe AKI.[17] However, the presence of CKD was not associated with increased severity of AKI in our study.

In agreement with other published reports,[14] we also observed significant differences in the causes between patients with CA-AKI and HA-AKI. Volume depletion contributed to significantly more cases of CA-AKI, while ATN was more common in HA-AKI. This should not come as a surprise, since it is well known that patients with HA-ARF are more likely to have more severe illness, and the HA-ARF include frequently postoperative ARF cases.[10]

The need for acute dialysis in patients with AKI ranges from 36% to 86%,[18,19] depending on the origin of the AKI and the hospital setting. A rate of 36% was reported in one community-based study,[19] while the rate was 46% to 86% in a hospital-based ICU study.[18] In our study we observed no significant differences between the numbers of patients requiring renal replacement therapy in both groups (20.7% in HA-AKI and 22.3% in CA-AKI).

Previous studies reported that RIFLE classification predicted increased length of stay, increased likelihood of discharge to rehabilitation facility, and increased mortality in patients with HA-AKI.[1,12,20-25] In the current study the length of hospital stay was no different between patients with CA-AKI and HA-AKI and the degree of renal dysfunction cannot predict the length of hospital stay alone in the both groups because there was a similar distribution of AKIN class.

AKI is an important contributor to CKD. Previous studies have highlighted increased risks of de novo CKD following episodes of AKI with incomplete recovery.[4,11,14,26,27] In the current study, patients with both CA-AKI and HA-AKI were found to have incomplete immediate recovery of renal function, based on discharge serum creatinine. We conclude that episodes of CA-AKI can also be a risk factor for the development or progression of CKD.

All notable adverse outcomes in AKI such as mortality occurred more frequently in HA-AKI. It has been previously noted that mortality in CA-AKI may be up to 20% lower than that of HA-AKI.[18,19] According to some recent reports, the mortality rate in CA-AKI ranged from 15% to 26%,[19] whereas the mortality rate in HA-AKI ranged from 25% to 70%.[18] Also, the mortality rates observed in our study were consistent with these published reports. In this study, although AKI severity and comorbidity had a similar distribution between CA-AKI and HA-AKI groups, the mortality rate was significantly higher in the HA-AKI group compared to AC-AKI.[13,14] Documented predictors of mortality such as oliguria, sepsis, multiorgan failure, and ICU stay or mechanical ventilation occurred more frequently in patients with HA-AKI.[24,28] In our study, we actually found the some finding, in fact, HA-AKI group had higher prevalence of mechanical ventilation (18.9% *vs.* 8.3% in CA-AKI group; p<0.04), higher rate of multiorgan failure (17% *vs*. 14%. p=NS), higher prevalence of anuria (15.1% *vs.* 8.3% p= NS) and a higher rate of ICU stay (22.7% *vs.* 9.6; p<0.05).

In the present study, having a long term following up of included patients would be relevant. It will allow us to determine renal long term outcome. This is a limitation for this study. However, we are confident about the results since the prospective

design we used is very accurate.

CONCLUSION

This current report is one of few prospective study comparing AC-AKI and AH-AKI. Our data suggest that CA-AKI is a common cause of AKI that is as severe as that seen in HA-AKI. CA-AKI has a significant impact on length of stay, mortality, and the development and/or progression of CKD. Development of strategies to limit the risk of CA-AKI such as high risk factor subject screening may have a significant impact on healthcare costs and patient's prognosis.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Research

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Extensive Search for Dry Weight: Should We Change the Strategy?

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ABSTRACT

Introduction: A wrong estimate of the dry weight in hemodialysis patients increases their morbidity and mortality. The aim of our study was to compare the results of the estimated dry weight using the clinical examination with the results of the lung ultrasound, impedance measurement, ultrasound of the inferior vena cava and B-type Natriuretic Peptide (BNP) assay.
Methods: A cross-sectional study was conducted in an hemodialysis center at Fez. The estimated dry weight of the patients was evaluated before and 30-60 minutes after the hemodialysis session using the four above-mentioned methods.
Results: The values, measured by the different techniques used, drop significantly after hemodialysis ($p<0.001$). The measurement studied before and after the hemodialysis, had shown a significant correlation between the results of the impedance measurement, lung ultrasound, the maximum and minimum of the Venous Collapsibility Index (VCI) index diameter as well as its collapsibility. However, no correlation was found between BNP levels and other methods. A significant difference between the results provided by the techniques studied and the results of the clinical evaluation was found in 84.4% of patients. In univariate analysis, only age was significantly shown as an associated factor with error estimation ($p<0.04$).
Conclusion: This study is one of the few studies using lung ultrasound to assess the hydration status of hemodialysis patients. It also showed a good correlation with other methods. The existence of a gap between the subjective and objective target weight suggests the usefulness of a systematic periodic use of bioimpedance and ultrasound techniques even if clinical symptoms are absent.

KEYWORDS: Dry weight; Hemodialysis; Bioelectrical impedance; Inferior vena cava diameter; Ultrasound lung; B-type natriuretic peptide.

ABBREVIATIONS: BNP: B-type Natriuretic Peptide; VCI: Venous Collapsibility; BIS: Bioimpedance spectroscopy; IVC: Inferior Vena Cava; HD: Hemodialysis; BCM: Body Composition Monitor.

INTRODUCTION

The reliable and reproducible estimate of dry weight in hemodialysis patients remains a clinical problem to date. Prolonged overestimation of dry weight causes hypertension, left ventricular hypertrophy and heart failure, while the underestimation is responsible for a chronic dehydration leading to the risk of hypotension.[1] Both complications have a significant impact on morbidity and mortality in hemodialysis patients.[2]

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Despite the huge progress achieved in the assessment of the adequacy of dialysis treatment in term of solutes purification; no measure allows, at the present time, to accurately assess the adequacy of the fluid balance.[3]

Most centers determine the ultrafiltration rate during the session based on the weight «target» as a reference. This represents the weight reached late in the session after normalization of the patient's extracellular volume. In other words, it is the weight that is associated with the absence of extracellular dehydration signs, or signs of hydrosodic retention.[4] However, this parameter is considered clinically very subjective, varying significantly, and imprecise since it does not take into account the changes in nutritional status, lean body mass, and the vascular refilling capacity of each patient.[5]

It is obvious that using better assessment methods of determining volume changes during hemodialysis are needed to adapt the goal for fluid removal so that the target weight later will always be close to the true dry weight of the patient. Such methods have evolved from clinical assessment to sophisticated systems of "biofeedback", which incorporate blood volume, ultrafiltration rate and conductivity, going through the use of Body Composition Analysis (Body Bioimpedance spectroscopy (BIS)), ultrasound of the vena cava, the serum markers and lung ultrasound.[6]

The objectives of our study are:

- To assess fluid status of chronic hemodialysis patients by using: lung ultrasound, Body bioimpedance spectroscopy (BIS), ultrasonography of the Inferior Vena Cava (IVC) and Natriurectic peptide type B dosage (BNP) assay,
- To measure the correlation between the results of the four methods,
- To compare the dry weight, determined by the objective methods mentioned above, with the one determined clinically,
- To identify associated factors with eventual errors in the clinical estimation of the dry weight.

MATERIALS AND METHODS

Study Design

This is a cross-sectional study, conducted during March 2014 in the hemodialysis center of Al Ghassani provincial Hospital in Fez.

Patients

Using an arteriovenous fistula, the patients included in this study were aged over 18, and have begun chronic hemodialysis since at least 3 months.

Were excluded from the study all the patients with the following criteria:

• An acute event (infectious episode or a hospitalization) within the 3 months preceding the study regardless of the cause.
• A lung disease with pulmonary fibrosis, or dyspnea stage IV of NYHA showing a heart failure that may affect the results of lung ultrasound regardless of the state of hydration.
• Inability to wear bioimpedance spectroscopy (BIS) (prostheses, pacemaker ...).

All our patients receive a conventional intermittent dialysis for two to three sessions per week, using low permeability polysulfone membranes with a standard bicarbonate dialysate. The Ultrafiltration rate is prescribed according to the interdialytic weight gains compared to the target weight clinically determined by the treating nephrologist.

Data Collection

The survey was carried out by a nephrologist not belonging to the team of hemodialysis center where the study is conducted. A pre-operating sheet was used for the collection of information.

In addition to demographic data and those related to kidney disease, comorbidities and dialysis prescription, we collected all episodes of intradialytic hypotension, cramps or postdialytic asthenia, during the last three sessions of hemodialysis.

The dry weight assessment parameters were measured in two phases: one hour before the Hemodialysis (HD) session and between 30 to 60 minutes following the end of the same session.

Therefore, the parameters collected are:

- Weight, under the usual conditions of the center using an electronic scale.
- The supine blood pressure measurement is done after 10 minutes rest, using a validated electronic device.

Bioimpedance spectroscopy (BIS): We used the BCM (Body Composition Monitor, Fresenius Medical Care®, Germany), dedicated to the analysis of body composition and nutritional status of patients. The impedance was performed to the patients, who were lying down flat in bed, after having rested immediately 10 minutes before and 30 to 60 minutes after the hemodialysis session. The electrodes were placed on the wrist of the contralateral arm of the Arteriovenous Fistula (AVF) and on the homolateral ankle.

Lung Ultrasound: Lung ultrasound was performed by the same trained nephrologist, who did not have access to patients' clinical data and also to the impedance results. The imaging was made by using an ultrasound (KOLTRON Magic Maestro) with a 7 Mhz vascular probe in order to look for an alveolar-intersti-

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tial syndrome characterized by the presence of specific artefacts called "B-lines" or "comet tails " which are proof of pneumonitis (congestion of the lungs) caused by fluid overload in hemodialysispatients.[7,8] Ultrasound examination was performed to the patients in supine position, with a longitudinal scan from the second to the fourth intercostal space of the left hemi-thorax and from the second to the fifth intercostal space of the right hemithorax at the medioclavicular and midaxillary lines of each side. B-lines were defined as a hyperechogenic linear artifact that are emerging from the pleural line, going to the bottom of the screen, and are being coherent with respiratory movements. The number of B-lines has been determined by the sum of the B-lines found in each examined site. Thus, the selected number reflects the extravascular accumulation of the liquid in the lung.

Ultrasound of the inferior vena cava (IVC): We used an ultrasound (KOLTRON Magic Maestro) with a 3.5 Mhz cardiac probe. The same trained operator explored the IVC within the sub-xiphoid window at 2.5 cm of the IVC-right atrial junction. The measure of the minimum diameter of IVC (DIVC min) was made during inspiration and during the expiration; the maximum diameter of the IVC (DIVC max) was measured.

Dosage of natriurectic peptide type B (BNP): We assayed the BNP immediately before and after the hemodialysis session using a patented enzyme immunoassay (TOSOH®).

STUDIED VARIABLES

Definitions

- The subjective target weight: it was the prescribed weight taken from the patient logbook, estimated by the attending nephrologist, and based on clinical criteria such as: weight, blood pressure, presence of edema or vascular congestion, as well as the weight on cardiac index measured by the chest x-ray.
- The objective Target weight: it was the determined weight based on the various performed techniques (Impedance, BNP, lung ultrasound, ultrasound of the inferior vena cava).
- Weight loss: is the difference between the weight before and after hemodialysis.

Impedance Results

The reference values determined by the impedance to define euvolemia in the normal population are within the range of -1.1 L to 1.1 L.[9] Referring to these values, we have classified our patients into three groups:

- Dehydrated patients if the fluid volume is less than the reference value-1.1 L
- Patients in euvolemia if the volume of fluid is within the reference range±1.1 L
- Patients in overload if the fluid volume is greater than the reference value+1.1 L.

Results of the Inferior Vena Cava Ultrasound

The index of the IVC diameter (iIVCD) was measured by dividing the IVCD maximal and IVCD minimal on body surface (Dubois formula) to obtain respectively the iIVCD max, and the iIVCD min.

The collapsibility index of the IVC (CiIVC) was calculated by using the following formula:

[(IVCD max - IVCD min)/IVCD max × 100].

Referring to the criteria of ultrasound,[10] we classified patients:

- Dehydrated if the iIVCD max <8 mm/m².
- Euvolemic if 8 mm /m²≤iIVCD max ≤11.5 mm/m².
- In overload if the iIVCD max >11.5 mm/m².

Results of Lung Ultrasound

Pulmonary congestion (Lung congestion) by fluid overload was retained in patients with the following characteristics:[11]

1. Scan which shows several lines "B": number >2 (criteria of the SFAR)
2. Positivity diffuse in more than one scans
3. Bilateral positivity

Biological Outcomes

For the BNP assay method used in our study, values that are below 120 pg/ml are considered as normal; whereas, those above 400 pg/ml are considered as high.[12] For the other biological parameters, we used the mean value of serum sodium, calcium, phosphate, CRP, hemoglobin, PTH and albuminemia in the last three months.

STATISTICAL ANALYSIS

The data were entered into an Excel sheet and analyzed using SPSS software Version 20. In the descriptive analysis, quantitative variables were expressed as mean±standard deviation and qualitative variables as percentages. The comparison of means was made using Student test; whereas, the comparison of percentages was performed using Chi-square test. To measure the correlation between the results of the four evaluated objective methods, we have used the bivariate correlation method and estimated the r coefficient for each correlation. Subsequently, three groups of patients were defined according to the difference between the objective target weight determined by the different methods used in our study and the subjective target weight predetermined clinically by the health care team:

- Group A: The objective target weight is less than the subjective target weight with a deviation of more than one kilogram
- Group B: The deviation between the objective and the sub-

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jective target weight does not exceed one kilogram. This is the standard acceptable gap in our study.
- Group C: The objective target weight is greater than the subjective target weight with a deviation of more than one kilogram.

An univariate analysis was performed to show the correlates of the subjective estimation error of the target weight.

ETHICAL CONSIDERATIONS

An informed consent for participating in the study was obtained from all patients. No invasive investigation was used. All additional costs associated with the study were funded by the research budget of the Nephrology Department of the University Hospital Hassan II of Fez.

RESULTS

We included 77 patients, aged 48.13±16 years with a sex ratio (M/F) of 1.1. The average length of hemodialysis was 10.1±0.5 years. Initial nephropathy was vascular, glomerular and diabetic in respectively 35%, 20% and 8.5% of cases. 44% of patients are hypertensive. Dyspnea was found in 35.1% of cases, mostly stage I (24.7%) and no patient had dyspnea stage III or IV. Anemia was found in 52.6% with a mean hemoglobin rate of 9.62±2.17 g/dl. The mean albumin rate was 39.73±7.5 g/l. Clinical, biological and demographic characteristics are presented in Table 1.

Parameters	N=77
Hypertension (%)	44
Cardiac ejection fraction (%)	66.5
Dyspnea stage (NYHA %) Stage I Stage II Stage III. IV	35.1 24.7 10.4 0
Intradialytic hypotension (%)	7.8%
Weekly sessions (%) 3 times 2 times	50.6% 49.4%
Residual diuresis (ml/j)	146±394
Rate UF/session (ml)	2500 IQR (2000-3100) Range (1000-4500)
Hemoglobin rate (g/dl)	9.6 IQR (8.0-11) Range (4.8-14.1)
Albumine rate (g/l)	40.9 IQR (36-44.9) Range (20.3-48)

Table 1: Baseline characteristics (mean±SD).

The values of fluid status assessment, which are measured by the impedance, the number of B-lines in lung ultrasound, the IVC index, and the BNP rate, decreased significantly ($p<0.001$) after hemodialysis compared to predialytic values (Table 2). The same results were shown when we consider the categories of each measurement method: in patients with fluid overload, the values of impedance, IVC, the number of B-lines and BNP decreased significantly subsequent to hemodialysis (Figure 1). On the other hand, in post dialysis, there were more patients who were classified hypovolemic by ultrasound of the IVC (57%) than by impedance (38%).

	Before HD	After HD	P
Bioimpedance (liter)	+1.2±1.2	-0.36±1.3	<0.001
Lung ultrasound Number of B-lines	4.4±3.4	1.3±1.6	<0.001
Ultrasound of VCI iDVCI max (mm) iDVCI min (mm) CVCIi %	 10.2±2.6 5.1±3.1 53.2±24.1	 7.6±2.6 2.4±3 75.1±29.2	 <0.001 <0.001 <0.001
BNP (pg/ml)	603±606.5	405.5±560.7	<0.001

VCI: Inferior vena cava; iDVCI: index of the inferior vena cava diameter; CVCI: Collapsibility index of the inferior vena cava; BNP: B natrialpeptid.

Table 2: Fluid status before and after hemodialysis session (mean±SD).

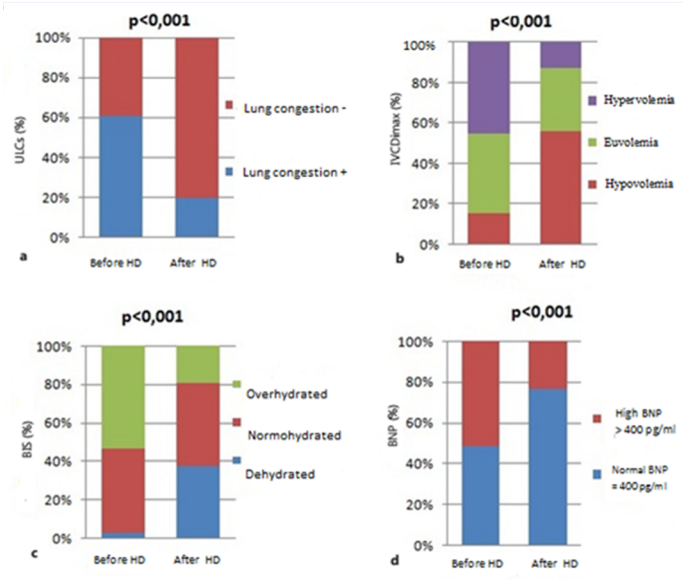

Figure 1: Distribution of groups according to fluid status determined by lung ultrasound comets (a) inferior vena cava diameter (b) bioimpedance spectroscopy (c) and b natrial peptid (d) before and after hemodialysis session.

The correlation analysis between the results of different techniques before and after hemodialysis is summarized in Table 3. There was a very significant correlation between the impedance, lung ultrasound, the index of the maximum and minimum IVC and its collapsibility both before and after hemodialysis session. However, there was not any significant correlation between BNP rate and other studied methods.

We also studied the correlation between the change of the ultrasound results and the movement of water during hemodialysis session expressed by weight loss. Only the reduction of the number of the B-lines was significantly correlated with weight loss (β coefficient=0.36, $p<0.005$) (Table 4).

In our study, only 15.6% of patients did not have a gap between the subjective target weight and objective target weight, while 84.4% of patients had a significant difference between the results provided by the techniques studied and the result of clini-

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	B-Lines	iDVCI min	iDVCI max	CVCIi	BNP
- Before hemodialysis session					
Over hydratation by bioimpedance	0.691**	0.372**	0.461**	-0.244*	0.08
B-Lines	_	0.610**	0.607**	-0.485**	0.095
iDVCI min	_	_	0.788**	-0.558**	0.052
iDVCI max	_	_	_	-0.916**	0.013
CVCIi	_	_	_	_	-0.005
BNP	_	_	_	_	_
- Afterhemodialysis session					
Over hydratation by bioimpedance	0.756**	0.559**	0.581**	-0.507**	0.128
B-Lines	_	0.679**	0.749**	-0.592**	0.101
iDVCI min	_	_	0.837**	-0.959**	0.001
iDVCI max		_	_	-0.737**	0.097
CVCIi	_	_	_	_	0
BNP	_	_	_	_	_
*0.001<p<0.05 **p<0.001					

VCI: Inferior vena cava; iDVCI: index of the inferior vena cava diameter; CVCI: Collapsibility index of the inferior vena cava; BNP: B natrial peptid.

Table 3: Correlation between different techniques before and after hemodialysis session.

Correlation between weight loss and:	Coefficient β	P
B-linesreduction (%)	0.36	0.005
DVCI max reduction (%)	0.12	NS
DVCI min reduction (%)	0.04	NS
CVCI reduction (%)	-0.11	NS

DVCI: the inferior vena cava diameter; CVCI: collapsibility of the inferior vena cava.

Table 4: Linear regression with weight loss.

cal evaluation. 70.1% of these patients had a negative gap (group A) and 14.3% of them had a positive gap (group C).

In the univariate analysis, several factors were studied in order to show correlates of these differences including: age, sex, comorbidities, length of hemodialysis, inflammation, anemia, nutritional status, left ventricular hypertrophy, systolic ejection fraction. Age was the only significant factor that was related to the differences since the patients with a negative gap (group A) had an average age of 47.2±12 years; whereas, the subjects with no gap (Group B) had an average age of 58±13 years and those with a positive gap (group C) had a mean age of 50.7±13.7 years (p<0.04).

DISCUSSION

This is a cross-sectional study conducted to compare firstly the different techniques of assessing water status before and after hemodialysis session, and secondly to assess hydration status of our patients and have a more objective view of their dry weight in order to establish a strategy to optimize their care.

All the techniques investigated in this study show that there is a reduction in overload after hemodialysis session, and there is a good correlation between these different methods except the BNP assay. This result fits in with the one found by F Basso, et al. in 2013.[13] Although, the new techniques are promising, they have important practical and theoretical limits. For example, skin lesions, wrongly placed electrode, electrical interference, and obesity are the limits of theimpedance.[6] In addition, the data of the impedance change 120 minutes after the end of hemodialysis.[14] Similarly, Agarwal, et al. has shown that the measurement of IVCD is a method that well reflects the intravascular volume but has a low sensitivity for detecting a change in the fluid in post-dialysis time.[15] Consistently, our results shown that inpost-dialysis, there are more patients classified hypovolemic by ultrasound measurements of the IVC than by conductivity measurement. This difference is due to the time required for transferring the fluid from the interstitial sector to the intravascular one "refilling". At the end of the hemodialysis session, a relative hypovolemia may exist. The conductivity measurements achieved just after the dialysis session, underestimate the degree of dehydration. While ultrasound of inferior vena cava (IVC) overestimates the degree of dehydration in these patients. The results obtained by these two techniques should be close enough if the measurements were made a few hours after hemodialysis session.[16] Among our hemodialysis patients, the rate of BNP is high in pre-dialysis, especially in patients suffering from over-

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load, and significantly reduces in post-dialysis time. However, it is not correlated with the results of the other methods. This could partly be explained by the existence of other determinants than the volume overload that may influence BNP rate in these patients, particularly any myocardial aggression.[17] On the other hand, this hormone is dialyzable with the membranes of high and low permeability.[18] This allows us to infer, as it has already been shown, that the dosage of the BNP does not have an interest in the evaluation of water status in hemodialysis patients,[19] since this assay does not distinguish between euvolemic and dehydrated patients.[20]

Lung ultrasound is a simple method, that is easy, inexpensive, without irradiation, andwhich can be used at the bedside of the patients.[21] Nevertheless, it is an operator-dependent method. Previously, it was shown that the number of B-lines was correlated to the extravascular water.[21] In our study, the correlation between weight loss and ultrasound data, showed that only the reduction of B-lines was significantly correlated; whereas, no correlation existed with the reduction of IVCD. This confirms that the two preceding techniques evaluate two different fluid compartments: the IVCD reflects the volume of intra-vascular water, and the number of B-lines reflects the volume of extravascular water. Thus, the IVCD is not sensitive in assessing rapid changes of fluids during hemodialysis,[22] whereas, lung ultrasound can be performed immediately after hemodialysis.[23]

At the end of this study, we had shown that a significant difference existed between the objective target weight and the subjective target weight. This confirms that the actual determination of the dry weight is difficult and the clinical estimation remains a non-specific method[3] and therefore insufficient. The underestimated dry weight in most of our young chronic hemodialysispatients had no clinical or interdialytic relevance. It misled the nephrologist in 70% of cases. This would be due to a better hemodynamic tolerance of Ultrafiltration or rather of dehydration in young patients who have a good cardiovascular condition. Studies have clearly shown an increased risk of death and cardiovascular events when intradialytic hypotension happens in hemodialysis patients in older population.[24] Young hemodialysis patients, asymptomatic despite the hypovolemia, are often underestimated in different studies. Cardiovascular morbidity and mortality risk deserves to be studied in this subgroup of patients. It also raises the question of the value of a periodic systematic use of impedance and ultrasound techniques in all hemodialysis patients even in the absence of a clinical anomaly.

CONCLUSION

This study is among the few studies that have used lung ultrasound to assess the state of hydration of hemodialysis patients. It allows us to show the right correlation between the results of this review and those of the impedance and the ultrasound of the IVC. The existence of a gap between the subjective target weight and the objective target weight suggests the incessant need for a coupling between these different techniques according to a strategy adapted to the characteristics of each patient.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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